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United States Patent [19]

Shaskan

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[54] **COMPOSITIONS COMPRISING NICOTINYLALANINE AND AN INHIBITOR OF GLYCINE CONJUGATION OR VITAMIN B6**

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[51] **Int. Cl.**[6] **C07D 213/79**; A01N 43/40; A61K 31/60

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[58] **Field of Search** 514/351, 353, 514/356

[56] **References Cited**

PUBLICATIONS

Chemical Abstracts AN 1977:118750, Yeh et al., Jan. 1977.

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[57] **ABSTRACT**

This invention relates to compositions comprising nicotinylalanine (NAL) and/or related analogues, and an inhibitor of glycine conjugation, either synthetic or naturally occurring. Vitamin B6 may also be present in the compositions of this invention in place of, or in addition to, the inhibitor of glycine conjugation. The compositions may be pharmaceutical in nature. The compositions are useful for inhibiting cellular poly(ADP-ribose) polymerase (PARP, PARS, poly (ADP-ribose) synthetase), an enzyme which causes cellular toxicity and which is activated in a variety of toxic and pathological conditions. PARP is inhibited by some metabolites of the tryptophan oxidative pathway, including nicotinamide, kynurenic acid and xanthurenic acid, which are induced by interferon-gamma. The NAL-containing compositions of the invention enhance the intracellular levels of these metabolites, and thereby augment the natural defense of interferon-induced inhibition of PARP. PARP is implicated in various pathological conditions, including neurodegenerative disorders, viral infections such as AIDS, autoimmune diseases and cancer. Accordingly, this invention also relates to methods of reducing cellular toxicity, and treating or preventing such diseases, by increasing cellular concentrations of nicotinamide, kynurenic acid and xanthurenic acid using the compositions of this invention.

67 Claims, 8 Drawing Sheets